

# Comment on “Elastic Membrane Deformations Govern Interleaflet Coupling of Lipid-Ordered Domains”

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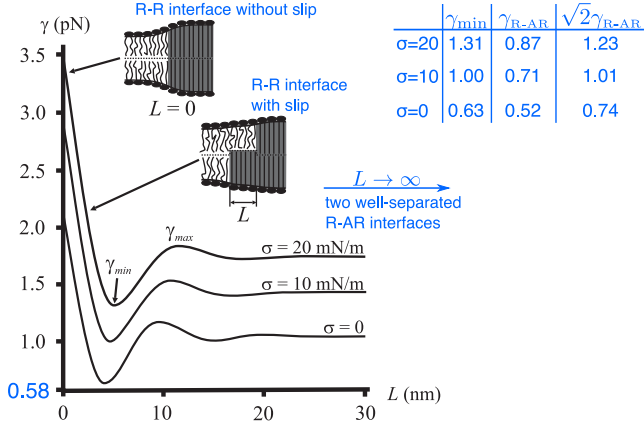


FIG. 1. Line tension versus slip length  $L$  [1], annotated (blue).  $\gamma(L \rightarrow \infty) = 2\gamma_{R-AR}$  (see text). An axis tick is corrected.

Galinzyanov et al. [1] find that line tension between thick liquid-ordered ( $L_o$ ) and thinner liquid-disordered ( $L_d$ ) registered lipid bilayer phases is minimised by an asymmetric “slip region”, length  $L \sim 5$  nm (Fig. 1). They claim that line tensions alone explain domain registration, without “direct” (area-dependent) inter-leaflet interaction [2, 3]. We show this is unfounded; without direct interaction their results would predict *antiregistration*, dependent on composition. To find equilibrium from line energies, line *tensions* must be combined with interfacial lengths for given states at given composition. This was not done in [1].

Fig. 2a shows “registered” (R) and “antiregistered” (AR) bilayer phases in  $(\phi^t, \phi^b)$  (top/bottom-leaflet composition) space [2–4]. We assume  $\phi^b = \phi^t \equiv \phi$  in each leaflet. “Domain registration” is R-R coexistence (Fig. 2a), with slip to minimise line tension (Fig. 1) [1].

Without direct inter-leaflet coupling, R and AR bulk free energies would be equal [3] so line energies alone would determine equilibrium. The authors claim perfect *antiregistration* (AR-AR state) is only possible for  $\phi = 1/2$ . They assume imperfect antiregistration involves *both* R-AR interfaces in Fig. 1. They find a minimum line tension  $\gamma_{\min}$ , and a limiting value  $\gamma_{\infty} \equiv \gamma(L \rightarrow \infty) > \gamma_{\min}$  as the two R-AR interfaces in Fig. 1 ( $L_d/L_d$  to AR, AR to  $L_o/L_o$ ) move apart. They claim that  $\gamma_{\infty} > \gamma_{\min}$  favours an R-R state. However,  $\phi \neq 1/2$  only forces one R phase (AR-AR-R state, Fig. 2a), and the line tension of *one* isolated R-AR interface in Fig. 1 is  $\gamma_{R-AR} \approx \gamma_{\infty}/2$ .

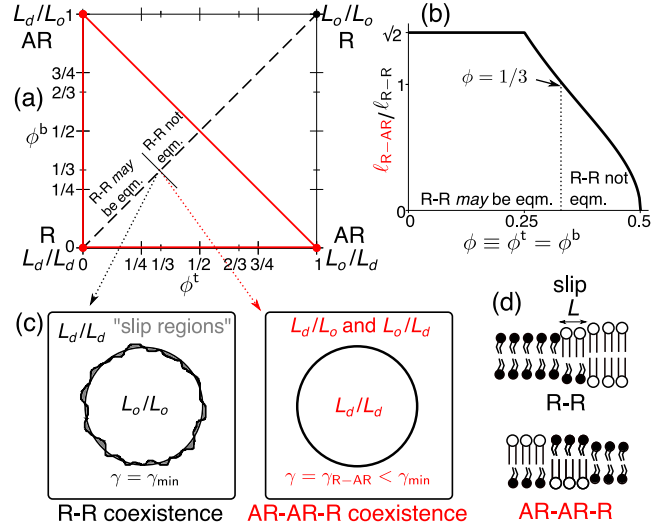


FIG. 2. (a) Partial diagram of two-phase R-R (black) and three-phase AR-AR-R (red) coexistences for  $\phi^b = \phi^t \equiv \phi < 1/2$  [the full diagram is symmetric under inversion through (0.5, 0.5) [4]]. (b) Minimal R-AR or R-R interface length, comparing AR-AR-R and R-R coexistence. (c) Morphology at  $\phi = 1/3$ , beyond which AR-AR-R decreases thickness-mismatched interface length. (d) R-R coexistence; AR-AR-R.

In R-R, an  $L_o/L_o$  droplet, area  $\phi A$ , circumference  $\ell_{R-R} = 2\sqrt{\pi\phi A}$  is surrounded by  $L_d/L_d$  (Fig. 2c,  $A =$  total area). The line energy is  $W_{R-R} = \ell_{R-R}\gamma_{\min}$ . For AR-AR-R, the area of  $L_o/L_d$  or  $L_d/L_o$  is  $2\phi A$ . [The equal-thickness phases are treated as a quasi-uniform single phase.] Hence, for  $\phi < 1/4$ ,  $L_d/L_d$  surrounds an AR domain ( $\ell_{R-AR} = 2\sqrt{2\pi\phi A}$ ), with  $W_{R-AR} = \ell_{R-AR}\gamma_{R-AR}$ .  $\ell_{R-AR} = \sqrt{2}\ell_{R-R}$  (Fig. 2b), so R-R would be equilibrium ( $W_{R-R} < W_{R-AR}$ ) if  $\gamma_{\min} < \sqrt{2}\gamma_{R-AR}$ . This holds for  $\sigma = 0$ , but not  $\sigma = 20$  mN/m (Fig. 1), and will depend on other parameters, e.g., the degree of hydrophobic mismatch.

For  $1/4 < \phi < 1/2$ , AR surrounds an  $L_d/L_d$  domain of  $\ell_{R-AR} = 2\sqrt{\pi(1-2\phi)A}$ . For  $1/3 < \phi < 1/2$  (by symmetry  $1/2 < \phi < 2/3$  [4]),  $\ell_{R-AR} < \ell_{R-R}$ ; R-R would not be equilibrium for  $\gamma_{R-AR} < \gamma_{\min}$ . Indeed, as  $\ell_{R-AR} \rightarrow 0$  ever higher  $\gamma_{R-AR}$  would be needed to stabilise R-R. A full calculation of  $\gamma_{R-AR}$  should use a single R-AR interface. Imposing flat boundary conditions could give an area-dependent cost, or make  $\gamma_{R-AR}$  depend on where the boundary conditions are enforced.

Upon reinstating direct, area-dependent inter-leaflet

coupling [undulations (see Reply) are one possible source], the *bulk* free energy of R is lower than AR, explaining equilibrium domain registration over all  $\phi$  [2–4].

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